IFNL3/4 polymorphisms are associated with AIDS-related Kaposi's sarcoma

Bibert, Stéphanie ; Wojtowicz, Agnieszka ; Taffé, Patrick ; Tarr, Philip E ; Bernasconi, Enos ; Furrer, Hansjakob ; Günthard, Huldrych F ; Hoffmann, Matthias ; Kaiser, Laurent ; Osthoff, Michael ; Fellay, Jacques ; Cavassini, Matthias ; Bochud, Pierre-Yves ; Swiss HIV Cohort Study

Abstract: BACKGROUND Kaposi's sarcoma (KS), the most common AIDS related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections. OBJECTIVES To analyze whether IFNL3/4 variants are associated with susceptibility to AIDS-related KS among men who have sex with men (MSM) enrolled in the Swiss HIV Cohort Study (SHCS). METHODS The risk of developing KS according to the carriage of IFNL3/4 SNPs rs8099917 and rs12980275 and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant co-variables. RESULTS KS was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both rs12980275 and rs8099917 were associated with an increased risk of KS (cumulative incidence 15% versus 10%, P = 0.01 and 16% versus 10%, P = 0.009 respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16% versus 10%, P = 0.01) but not the less active S70 (cumulative incidence 11% versus 10%, P = 0.7) form of IFNL4 were associated with an increased risk of KS, compared to those predicted not to produce IFNL4.The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median CD4 T-cell count nadir and CD4 slopes (HR = 1.43, 95% confidence interval 1.06-1.93, P = 0.02 for IFLN P70 versus no IFNL4). CONCLUSION This study reports for the first time an association between IFNL3/4 polymorphisms and susceptibility to AIDS-related KS.

DOI: https://doi.org/10.1097/QAD.0000000000002004

AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000002004

IFNL3/4 polymorphisms are associated with AIDS-related Kaposi's sarcoma

IFNL3/4 polymorphism and Kaposi's sarcoma

Stéphanie BIBERT[1], Agnieszka WOJTOWICZ[1], Patrick TAFFÉ[2], Philip E. TARR[3], Enos BERNASCONI[4], Hansjakob FURRER[5], Huldrych F. GÜNTHARD[6, 7], Matthias HOFFMANN[8], Laurent KAISER [9], Michael OSTHOFF[10], Jacques FELLAY[11, 12], Matthias CAVASSINI[1,], Pierre-Yves BOCHUD[1,**] and the Swiss HIV Cohort Study[†]

[1] Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, Lausanne, Switzerland
[2] Institute for Social and Preventive Medicine, University (IUMSP), Lausanne University Hospital, Lausanne, Switzerland
[3] Department of Medicine, Kantonspital Baselland, University of Basel, Bruderholz, Switzerland
[4] Division of Infectious diseases, Regional hospital of Lugano, Lugano, Switzerland
[5] Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland
[6] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[7] Institute of Medical Virology, University of Zurich, Zurich, Switzerland
[8] Division of Infectious Diseases and Hospital Epidemiology, Department of Internal Medicine, Cantonal Hospital St.Gallen, St.Gallen, Switzerland
[9] Laboratory of Virology, Division of Infectious Diseases and Division of Laboratory Medicine, University Hospital of Geneva and Medical School, University of Geneva, Geneva, Switzerland
[10] Division of Infectious Diseases and Hospital Epidemiology and Department of Internal Medicine, University Hospital Basel, Basel, Switzerland
[11] Global Health Institute, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
[12] Precision Medicine unit, Lausanne University Hospital, Lausanne, Switzerland

† Members of the Swiss HIV Cohort Study group are listed in the appendix

** Correspondence: Pierre-Yves Bochud, MD
Infectious Diseases Service
CHUV
Rue du Bugnon 46
1011 Lausanne, SWITZERLAND

Email: Pierre-Yves.Bochud@chuv.ch
Phone: ++41 21 314 43 79
Fax: ++41 21 314 40 60

Abstract

Background: Kaposi's sarcoma (KS), the most common AIDS related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections.

Objectives: To analyze whether *IFNL3/4* variants are associated with susceptibility to AIDS-related KS among men who have sex with men (MSM) enrolled in the Swiss HIV Cohort Study (SHCS).

Methods: The risk of developing KS according to the carriage of *IFNL3/4* SNPs *rs8099917* and *rs12980275* and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant co-variables.

Results: KS was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both *rs12980275* and *rs8099917* were associated with an increased risk of KS (cumulative incidence 15% versus 10%, P=0.01 and 16% versus 10%, P=0.009 respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16% versus 10%, P=0.01) but not the less active S70 (cumulative incidence 11% versus 10%, P=0.7) form of IFNL4 were associated with an increased risk of KS, compared to those predicted not to produce IFNL4.

The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median $CD4^+$ T-cell count nadir and $CD4^+$ slopes (HR=1.43, 95% confidence interval 1.06-1.93, P=0.02 for IFLN P70 versus no IFNL4).

Conclusion: This study reports for the first time an association between *IFNL3/4* polymorphisms and susceptibility to AIDS-related KS.

Keywords: Kaposi's sarcoma, polymorphism, immunogenetics, IFNL3, AIDS, HIV

Introduction

Kaposi's sarcoma (KS) was initially described by Moritz Kaposi in 1872 as a rare and relatively indolent angioproliferative neoplasm affecting elderly men from countries surrounding the Mediterranean Sea (classical form of KS) [1]. Another form was described in sub-Saharan Africa in the 1950s, which affects middle aged adults and children (endemic form of KS) [2]. In 1981, a potentially fatal form of KS was described among young homosexual men as a characteristic feature of the AIDS epidemics (epidemic form of KS), a population in which it still represents one of the most common AIDS related cancer [3-8]. An invasive form can also affect patients with non-AIDS immune suppression, in particular solid organ transplant (SOT) recipients (iatrogenic form of KS, reviewed in [2]).

While the four epidemiological forms of KS share the same histological characteristics [9] and are all subsequent to human herpes virus 8 (HHV-8) infection [10, 11], the development of distinct clinical features seems to rely on a combination of host and environmental factors. While HIV- or drug-related immune suppression is inherent to the epidemic and iatrogenic forms (AIDS and SOT), genetic predisposition may be required for the classical (Mediterranean and Jewish ancestry) [12-14] and endemic forms (Sub-Saharan Africa) [15]. Hormonal factors [16-19] have been proposed to explain the male predominance of all forms of Kaposi sarcoma. Environmental conditions relative to potential routes of infection (soil, animal vectors) have been proposed to influence susceptibility to different forms of KS [20-25]. While viral factors may influence clinical presentation, evidence for a definite link between a specific subtype strain and a KS type is still lacking [26-29].

Several investigators have analyzed the role of host genetic factors in susceptibility to KS within a given populations at risk. The most relevant was a polymorphism within the *IL-6* promoter, which was consistently more frequent among KS patients versus controls in two cohorts of AIDS patients [30, 31] and a small cohort of SOT patients [32]. Polymorphisms in other candidate genes (e.g. MHC- or cytokines/chemokines-related genes) were associated with KS in studies of AIDS patients [31, 33-35] and two studies including patients with the classical form of KS [36, 37].

Single nucleotide polymorphisms (SNPs) in the region encoding for interferon lambda 3 (IFNL3 previously named IL-28B) and interferon lambda 4 (*IFNL4*) represent major factors in the ability of individuals to clear HCV [38-41]. They determine different haplotypic combinations (diplotypes) based on their capacity to produce IFNL4, i.e. no production versus production as an active P70 or less active S70 form [42-44]. *IFNL3/4* SNPs are increasingly known to influence the susceptibility to or the clinical course of infections due to viruses other than HCV, including herpes viruses such as CMV and EBV [45-47]. Here, we hypothesize that *IFNL3/4* polymorphisms influence the risk to develop KS in AIDS patients.

Material and Methods

Study patients. The Swiss HIV Cohort Study (SHCS) is an ongoing multicenter prospective study of HIV-infected patients enrolled at seven major Swiss hospitals and their local affiliated centers since 1988 [48]. For the present study, Caucasian men who have sex with men (MSM) with available DNA for genotyping and a written informed consent for genetic studies were included. In order to account for the time at risk, only patients with an estimated date of HIV infection were selected [49]. Demographic characteristics including age, duration of HIV

infection, CD4 T-cell count nadir, other opportunistic infections, HIV maximal viral load and HAART use were extracted from the SHCS clinical database. Kaposi sarcoma was defined according to predefined clinical and histological criteria.

SNP genotyping. Genomic DNA isolated either from blood or cell pellets was genotyped for haplotype tagging SNPs *rs8099917* and *rs12980275* using a customized GoldenGate Genotyping Assay on Veracode® platform (Illumina ®, San Diego, CA, USA). These SNPs were used as surrogates for rs368234815 and rs117648444, respectively, based on previously published LD values, which were shown to determine the three main diplotypic forms of IFNL4. (refs)

Statistical analysis. Statistical analyses were performed using Stata (version 14.2, StataCorp LP, College Station, TX). Hardy-Weinberg equilibrium (HWE) was verified using the program genhw implemented in Stata. Haplotypes were inferred using the Phased and grouped according their ability to express the different forms of IFNL3/4 as described previously [43]. The association of *IFNL3/4* polymorphisms with Kaposi's sarcoma was assessed by 25 year-cumulative incidence curves as well as uni- and multivariable Cox regression models, using the estimated date of HIV infection as a starting point, with censoring at death and/or lost follow-up. Stepwise (i.e. backward) regression ($P<0.1$) was used to determine which variables were independently associated with the endpoint. The proportional hazard assumption was verified by using the stphtest command implemented in Stata. Estimated dates of HIV infection and CD4 slopes in both incident and prevalent cases were obtained by using a joint back calculation model as described previously [50].

Results

The study included 2558 MSM patients among whom 221 developed KS (8.6%, **Supplementary Table 1,** http://links.lww.com/QAD/B360). Considering the whole patient, the median age at estimated date of HIV infection was 34 (interquartile range, IQR=13). The median $CD4^+$ T cells nadir was 181 cells/mm^3 (IQR=174) and the maximal HIV RNA viral load 5.12 log_{10} copies/ml (IQR=0.85). Most individuals started HAART therapy during follow-up (97%). An active HBV infection was recorded in 10% of patients and HCV serology was positive in 8%.

The minor allele frequencies (MAFs) of IFNL3/4 *rs12980275* and *rs8099917* were 0.30 and 0.20, respectively, and both were at HWE. Carriage of *rs12980275* and *rs8099917* were both associated with an increased risk of KS (CI 15% versus 10%, P=0.01 and CI 16% versus 10%, P=0.009, respectively, **Figure 1**). Diplotypes predicted to produce the active P70 form of IFNL4, but not those predicted to produce the less active S70 form were associated with an increased risk of KS, compared to diplotypes not producing IFNL4 (CI 16% versus 10%, P=0.01 and CI 11% versus 10%, P=0.7, respectively)

The association between IFNL4P70-producing diplotypes and KSA remained significant in a multivariate Cox regression model, accounting for age at infection, HAART, median $CD4^+$ T-cell count nadir and $CD4^+$ slopes [(hazard ratio 1.43, 95% confidence interval (CI) 1.06-1.93, P=0.02), **Table 1**].

Discussion

Polymorphisms in the region encoding for IFNL3 and 4 have been identified for their major role in the ability of individuals to clear HCV. Increasing evidence suggests that such polymorphisms can also influence the clinical course of infections due to viruses other than HCV [51, 52], in particular those from the Herpesviridae family (CMV [45, 46], EBV [47] and HSV [53]). In this study, we report for the first time an association between *IFNL3/4* polymorphisms and susceptibility to Kaposi's sarcoma among HIV-infected MSM.

An increasing number of *in vitro* studies support the role of IFNL in the immunopathogenesis of viral infections due to viruses other than HCV. A series of cell culture-based models have shown that IFNL3/4 controls the replication of viruses such as human [54] and murine CMV [55], HSV2 [56], HBV [57], dengue virus [58], human metapneumovirus (hMPV) [59], influenza virus [60-62], lymphocytic choriomeningitis virus (LCMV) [63] and Sendai virus [64]. While no studies have analyzed the direct role of IFNL on HHV-8 replication, the involvement of IFNL in its immunopathogenesis is supported indirectly by at least two studies. Those showed that HHV-8 can inhibit IFN transcription by the production of interferon regulatory factor (IRF) homologues as well as block the expression of interferon stimulating genes (ISGs) through JAK-STAT pathway interference [65, 66].

Haplotypic combinations predicted to produce the P70 active, but not the S70 less active form of IFNL4, were associated with an increased risk of KS. This is consistent with the association reported in other viral infections; SNPs encoding or tagging the P70 IFNL4 induce a higher susceptibility to HCV [42, 44], CMV [45, 46], EBV [47] and HSV [53]. This paradoxical effect

of IFNL4 may rely on at least 3 different mechanisms. First, IFNL4 may compete with the other IFNLs through a mechanisms involving the overexpression of its IFNLR1 subunit [67]. Second, IFNL4 may induce a refractory state of the pathway due to persistent ISG expression [43]. Third, individuals expressing the active form of IFNL4 may in return produce lower amount of IFNL3, with subsequent reduced ISG expression [42, 68, 69]. The resulting balance between IFNL3 and IFNL4 expression may be particularly relevant in KS lesions, given the presence of numerous recruited plasmacytoid dendritic cells (pDC), which represent the most important producer of these cytokines [70].

Beyond antiviral properties, IFNLs may also exert anti-tumoral activities including a growth inhibitory effect and apoptosis of tumor cells, as recently described in culture of melanoma [71], lung adenocarcinoma [72, 73], neuroendocrine cancer [74], colorectal carcinoma [75], esophageal carcinoma [76] and hepatocellular carcinoma [77] cells or in mouse models of melanoma [78], colon adenocarcinoma [78] and fibrosarcoma [79]. In humans, the expression of IFNL1 has been negatively correlated with the progression of cervical cancer due to papilloma virus [80], suggesting a potential role of this cytokine in cancer immunity. Altogether, these data suggest that polymorphisms in IFNLs may not only influence the immunity against HHV-8, but also immunity against KS cancer cells.

Like most genetic association studies, our study performed on HIV-infected MSM is constrained by some limitations. Data on HHV-8 sero-prevalence are not available in the SHCS cohort, thereby preventing analyses limited to patients with Kaposi sarcoma but excluding HHV-8 positive individuals who did not develop KS. This limitation may be at least in part compensated by the fact that the prevalence of HHV-8 among MSM is elevated [81, 82] and that the

prevalence of KS and HHV-8 is very well correlated in HIV-infected populations [83-85]. Most likely the currently chosen analytic approach would under- but not overestimated the effect of IFL polymorphisms.

In summary, our data show an association between *IFNL3/4* polymorphism and the development of KS among HIV+ MSM patients. This new finding confirms that IFNLs mediate anti-viral responses against a growing range of viruses.

Acknowledgements. The authors thank all patients from the SHCS, as well as collaborators from the clinical, laboratory and data centers and all study nurses.

Financial support. PYB is supported by the Swiss National Science Foundation (324730_165954 and 33IC30_179636), the Leenaards Foundation, the Santos-Suarez Foundation and the Loterie Romande. PYB is recipient of a Mérieux research grant. Furthemore, this project was supported by SHCS project No 613. The Swiss HIV Cohort Study is supported by the Swiss National Science Foundation (grant #177499), by SHCS project #803 and by the SHCS research foundation.

Author's contributions.

SB performed sample management, DNA extraction, candidate SNP genotyping, statistical analysis and wrote the manuscript.

AW performed SNP genotyping for the SHCS patients and data management.

PT contributed to statistical analyses.

Members of the SHCS group including, PET, EB, HF, HFG, MH, LK, MO, JF, MC were directly involved in the clinical care of SHCS patients and data acquisition.

PYB designed the SHCS genetic project, obtained funding, supervised genotyping, performed data management and statistical analysis and wrote the manuscript.

All authors critically revised the manuscript.

Appendix. The members of the Swiss HIV Cohort Study are: Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

References

1. Kaposi M. Idiopathisches multiples Pigmentsarcom der Haut. Arch Dermatol Syphilol. 1872;4:265.

2. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nature reviews Cancer. 2010;10(10):707-19. doi: 10.1038/nrc2888. PubMed PMID: 20865011.

3. Goedert JJ. The epidemiology of acquired immunodeficiency syndrome malignancies. Semin Oncol. 2000;27(4):390-401. Epub 2000/08/19. PubMed PMID: 10950365.

4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59-67. doi: 10.1016/S0140-6736(07)61050-2. PubMed PMID: 17617273.

5. Ledergerber B, Telenti A, Egger M. Risk of HIV related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. Swiss HIV Cohort Study. Bmj. 1999;319(7201):23-4. PubMed PMID: 10390454; PubMed Central PMCID: PMC28149.

6. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA : the journal of the American Medical Association. 1999;282(23):2220-6. Epub 1999/12/22. PubMed PMID: 10605973.

7. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. British journal of cancer. 2008;99(5):800-4. doi: 10.1038/sj.bjc.6604520. PubMed PMID: 18665172; PubMed Central PMCID: PMCPMC2528138.

8. Sullivan SG, Hirsch HH, Franceschi S, Steffen I, Amari EB, Mueller NJ, et al. Kaposi sarcoma herpes virus antibody response and viremia following highly active antiretroviral therapy in the Swiss HIV Cohort study. AIDS. 2010;24(14):2245-52. Epub 2010/06/15. doi: 10.1097/QAD.0b013e32833b7830. PubMed PMID: 20543658.

9. Ablashi DV, Chatlynne LG, Whitman JE, Jr., Cesarman E. Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases. Clin Microbiol Rev. 2002;15(3):439-64. Epub 2002/07/05. PubMed PMID: 12097251; PubMed Central PMCID: PMCPMC118087.

10. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266(5192):1865-9. PubMed PMID: 7997879.

11. Russo JJ, Bohenzky RA, Chien MC, Chen J, Yan M, Maddalena D, et al. Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proceedings of the National Academy of Sciences of the United States of America. 1996;93(25):14862-7. Epub 1996/12/10. PubMed PMID: 8962146; PubMed Central PMCID: PMCPMC26227.

12. Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, et al. HHV-8-associated Kaposi sarcoma in a child with IFNgammaR1 deficiency. J Pediatr. 2004;144(4):519-23. Epub 2004/04/08. doi: 10.1016/j.jpeds.2003.11.012. PubMed PMID: 15069403.

13. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, et al. Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. The Journal of experimental medicine. 2010;207(11):2307-12. Epub 2010/09/30. doi: 10.1084/jem.20101597. PubMed PMID: 20876309; PubMed Central PMCID: PMC2964585.

14. Byun M, Ma CS, Akcay A, Pedergnana V, Palendira U, Myoung J, et al. Inherited human OX40 deficiency underlying classic Kaposi sarcoma of childhood. The Journal of experimental medicine. 2013;210(9):1743-59. Epub 2013/07/31. doi: 10.1084/jem.20130592. PubMed PMID: 23897980; PubMed Central PMCID: PMCPMC3754857.

15. Aavikko M, Kaasinen E, Nieminen JK, Byun M, Donner I, Mancuso R, et al. Whole-Genome Sequencing Identifies STAT4 as a Putative Susceptibility Gene in Classic Kaposi Sarcoma. J Infect Dis. 2015;211(11):1842-51. doi: 10.1093/infdis/jiu667. PubMed PMID: 25492914.

16. Ziegler JL, Katongole-Mbidde E, Wabinga H, Dollbaum CM. Absence of sex-hormone receptors in Kaposi's sarcoma. Lancet. 1995;345(8954):925. PubMed PMID: 7535877.

17. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev. 2000;24(6):627-38. Epub 2000/08/15. PubMed PMID: 10940438.

18. Bouscarat F, Dazza MC, Melchior JC, Bouvet E. Kaposi's sarcoma and sex hormones. AIDS. 1997;11(5):687-8. Epub 1997/04/01. PubMed PMID: 9108954.

19. Lunardi-Iskandar Y, Bryant JL, Blattner WA, Hung CL, Flamand L, Gill P, et al. Effects of a urinary factor from women in early pregnancy on HIV-1, SIV and associated disease. Nat Med. 1998;4(4):428-34. Epub 1998/04/18. PubMed PMID: 9546788.

20. Ascoli V, Zambon P, Manno D, Guzzinati S, Zorzi M, Arca B, et al. Variability in the incidence of classic Kaposi's sarcoma in the Veneto region, Northern Italy. Tumori. 2003;89(2):122-4. Epub 2003/07/05. PubMed PMID: 12841656.

21. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. Br J Cancer. 1998;78(11):1521-8. Epub 1998/12/04. PubMed PMID: 9836488; PubMed Central PMCID: PMCPMC2063225.

22. Ziegler JL. Endemic Kaposi's sarcoma in Africa and local volcanic soils. Lancet. 1993;342(8883):1348-51. Epub 1993/11/27. PubMed PMID: 7901641.

23. Montella M, Franceschi S, Geddes M, Arniani S, Cocchiarella G. Classic Kaposi's sarcoma and volcanic soil in southern Italy. Lancet. 1996;347(9005):905. Epub 1996/03/30. PubMed PMID: 8622424.

24. Simonart T. Role of environmental factors in the pathogenesis of classic and African-endemic Kaposi sarcoma. Cancer Lett. 2006;244(1):1-7. doi: 10.1016/j.canlet.2006.02.005. PubMed PMID: 16542773.

25. Henke-Gendo C, Schulz TF. Transmission and disease association of Kaposi's sarcoma-associated herpesvirus: recent developments. Curr Opin Infect Dis. 2004;17(1):53-7. Epub 2004/04/20. PubMed PMID: 15090892.

26. Hsu YH, Kuo WL, Su IJ. Clinicopathologic study of Kaposi's sarcoma and strain analysis of human herpesvirus 8 (HHV-8) DNA in the Hua-Lien area of eastern Taiwan. J Formos Med Assoc. 2001;100(7):449-54. Epub 2001/10/03. PubMed PMID: 11579609.

27. Kakoola DN, Sheldon J, Byabazaire N, Bowden RJ, Katongole-Mbidde E, Schulz TF, et al. Recombination in human herpesvirus-8 strains from Uganda and evolution of the K15 gene. J Gen Virol. 2001;82(Pt 10):2393-404. Epub 2001/09/20. doi: 10.1099/0022-1317-82-10-2393. PubMed PMID: 11562533.

28. Lacoste V, Judde JG, Briere J, Tulliez M, Garin B, Kassa-Kelembho E, et al. Molecular epidemiology of human herpesvirus 8 in africa: both B and A5 K1 genotypes, as well as the M and P genotypes of K14.1/K15 loci, are frequent and widespread. Virology. 2000;278(1):60-74. Epub 2000/12/09. doi: 10.1006/viro.2000.0629. PubMed PMID: 11112482.

29. Stebbing J, Wilder N, Ariad S, Abu-Shakra M. Lack of intra-patient strain variability during infection with Kaposi's sarcoma-associated herpesvirus. Am J Hematol. 2001;68(2):133-4. Epub 2001/09/18. PubMed PMID: 11559954.

30. Foster CB, Lehrnbecher T, Samuels S, Stein S, Mol F, Metcalf JA, et al. An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus. Blood. 2000;96(7):2562-7. PubMed PMID: 11001912.

31. Aissani B, Wiener HW, Zhang K, Kaslow RA, Ogwaro KM, Shrestha S, et al. A candidate gene approach for virally induced cancer with application to HIV-related Kaposi's sarcoma. Int J Cancer. 2014;134(2):397-404. doi: 10.1002/ijc.28351. PubMed PMID: 23818101; PubMed Central PMCID: PMCPMC4007164.

32. Gazouli M, Zavos G, Papaconstantinou I, Lukas JC, Zografidis A, Boletis J, et al. The interleukin-6-174 promoter polymorphism is associated with a risk of development of Kaposi's sarcoma in renal transplant recipients. Anticancer research. 2004;24(2C):1311-4. PubMed PMID: 15154666.

33. Gaya A, Esteve A, Casabona J, McCarthy JJ, Martorell J, Schulz TF, et al. Amino acid residue at position 13 in HLA-DR beta chain plays a critical role in the development of Kaposi's sarcoma in AIDS patients. AIDS. 2004;18(2):199-204. PubMed PMID: 15075536.

34. Aissani B, Boehme AK, Wiener HW, Shrestha S, Jacobson LP, Kaslow RA. SNP screening of central MHC-identified HLA-DMB as a candidate susceptibility gene for HIV-related Kaposi's sarcoma. Genes Immun. 2014;15(6):424-9. doi: 10.1038/gene.2014.42. PubMed PMID: 25008864; PubMed Central PMCID: PMC4174341.

35. Lehrnbecher TL, Foster CB, Zhu S, Venzon D, Steinberg SM, Wyvill K, et al. Variant genotypes of FcgammaRIIIA influence the development of Kaposi's sarcoma in HIV-infected men. Blood. 2000;95(7):2386-90. PubMed PMID: 10733511.

36. Brown EE, Fallin D, Ruczinski I, Hutchinson A, Staats B, Vitale F, et al. Associations of classic Kaposi sarcoma with common variants in genes that modulate host immunity. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2006;15(5):926-34. doi: 10.1158/1055-9965.EPI-05-0791. PubMed PMID: 16702372.

37. Tornesello ML, Buonaguro L, Cristillo M, Biryahwaho B, Downing R, Hatzakis A, et al. MDM2 and CDKN1A gene polymorphisms and risk of Kaposi's sarcoma in African and Caucasian patients. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals. 2011;16(1):42-50. doi: 10.3109/1354750X.2010.525664. PubMed PMID: 20979563.

38. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399-401. PubMed PMID: 19684573.

39. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nature genetics. 2009;41(10):1100-4. PubMed PMID: 19749758.

40. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nature genetics. 2009;41(10):1105-9. PubMed PMID: 19749757.

41. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology. 2010;138(4):1338-45, 45 e1-7. Epub 2010/01/12. doi: 10.1053/j.gastro.2009.12.056. PubMed PMID: 20060832.

42. Bibert S, Roger T, Calandra T, Bochud M, Cerny A, Semmo N, et al. IL28B expression depends on a novel TT/-G polymorphism which improves HCV clearance prediction. The Journal of experimental medicine. 2013;210(6):1109-16. doi: 10.1084/jem.20130012. PubMed PMID: 23712427; PubMed Central PMCID: PMC3674704.

43. Terczynska-Dyla E, Bibert S, Duong FH, Krol I, Jorgensen S, Collinet E, et al. Reduced IFNlambda4 activity is associated with improved HCV clearance and reduced expression of interferon-stimulated genes. Nature communications. 2014;5:5699. doi: 10.1038/ncomms6699. PubMed PMID: 25534433.

44. Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nature genetics. 2013;45(2):164-71. Epub 2013/01/08. doi: 10.1038/ng.2521. PubMed PMID: 23291588.

45. Manuel O, Wojtowicz A, Bibert S, Mueller NJ, van Delden C, Hirsch HH, et al. Influence of IFNL3/4 polymorphisms on the incidence of cytomegalovirus infection after solid-organ transplantation. J Infect Dis. 2015;211(6):906-14. doi: 10.1093/infdis/jiu557. PubMed PMID: 25301956.

46. Bibert S, Wojtowicz A, Taffe P, Manuel O, Bernasconi E, Furrer H, et al. The IFNL3/4 DeltaG variant increases susceptibility to cytomegalovirus retinitis among HIV-infected patients. AIDS. 2014;28(13):1885-9. doi: 10.1097/QAD.0000000000000379. PubMed PMID: 25259701.

47. Akay E, Patel M, Conibear T, Chaggar T, Haque T. Interleukin 28B gene polymorphisms and Epstein-Barr virus-associated lymphoproliferative diseases. Intervirology. 2014;57(2):112-5. doi: 10.1159/000357326. PubMed PMID: 24480970.

48. Swiss HIVCS, Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Gunthard HF, et al. Cohort profile: the Swiss HIV Cohort study. International journal of epidemiology. 2010;39(5):1179-89. Epub 2009/12/02. doi: 10.1093/ije/dyp321. PubMed PMID: 19948780.

49. Taffe P, May M, Swiss HIVCS. A joint back calculation model for the imputation of the date of HIV infection in a prevalent cohort. Statistics in medicine. 2008;27(23):4835-53. Epub 2008/04/30. doi: 10.1002/sim.3294. PubMed PMID: 18444229.

50. Loeuillet C, Deutsch S, Ciuffi A, Robyr D, Taffe P, Munoz M, et al. In vitro whole-genome analysis identifies a susceptibility locus for HIV-1. PLoS biology. 2008;6(2):e32. Epub 2008/02/22. doi: 10.1371/journal.pbio.0060032. PubMed PMID: 18288889; PubMed Central PMCID: PMC2245987.

51. Trevino A, Lopez M, Vispo E, Aguilera A, Ramos JM, Benito R, et al. Development of tropical spastic paraparesis in human T-lymphotropic virus type 1 carriers is influenced by interleukin 28B gene polymorphisms. Clin Infect Dis. 2012;55(1):e1-4. doi: 10.1093/cid/cis343. PubMed PMID: 22460962.

52. Angulo J, Pino K, Echeverria-Chagas N, Marco C, Martinez-Valdebenito C, Galeno H, et al. Association of Single-Nucleotide Polymorphisms in IL28B, but Not TNF-alpha, With Severity of Disease Caused by Andes Virus. Clin Infect Dis. 2015;61(12):e62-9. Epub 2015/09/24. doi: 10.1093/cid/civ830. PubMed PMID: 26394672; PubMed Central PMCID: PMCPMC4657541.

53. Griffiths SJ, Koegl M, Boutell C, Zenner HL, Crump CM, Pica F, et al. A systematic analysis of host factors reveals a Med23-interferon-lambda regulatory axis against herpes simplex virus type 1 replication. PLoS pathogens. 2013;9(8):e1003514. doi: 10.1371/journal.ppat.1003514. PubMed PMID: 23950709; PubMed Central PMCID: PMCPMC3738494.

54. Egli A, Levin A, Santer DM, Joyce M, O'Shea D, Thomas BS, et al. Immunomodulatory Function of Interleukin 28B during primary infection with cytomegalovirus. J Infect Dis. 2014;210(5):717-27. Epub 2014/03/13. doi: 10.1093/infdis/jiu144. PubMed PMID: 24620020.

55. Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, et al. IL-28A and IL-29 mediate antiproliferative and antiviral signals in intestinal epithelial cells and murine CMV infection increases colonic IL-28A expression. American journal of physiology Gastrointestinal and liver physiology. 2005;289(5):G960-8. Epub 2005/07/30. doi: 10.1152/ajpgi.00126.2005. PubMed PMID: 16051921.

56. Zhou L, Li JL, Zhou Y, Liu JB, Zhuang K, Gao JF, et al. Induction of interferon-lambda contributes to TLR3 and RIG-I activation-mediated inhibition of herpes simplex virus type 2 replication in human cervical epithelial cells. Mol Hum Reprod. 2015;21(12):917-29. Epub 2015/10/28. doi: 10.1093/molehr/gav058. PubMed PMID: 26502803; PubMed Central PMCID: PMCPMC4664393.

57. Robek MD, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. Journal of virology. 2005;79(6):3851-4. doi: 10.1128/JVI.79.6.3851-3854.2005. PubMed PMID: 15731279; PubMed Central PMCID: PMC1075734.

58. Palma-Ocampo HK, Flores-Alonso JC, Vallejo-Ruiz V, Reyes-Leyva J, Flores-Mendoza L, Herrera-Camacho I, et al. Interferon lambda inhibits dengue virus replication in epithelial cells. Virology journal. 2015;12:150. Epub 2015/09/29. doi: 10.1186/s12985-015-0383-4. PubMed PMID: 26411318; PubMed Central PMCID: PMCPMC4584467.

59. Banos-Lara Mdel R, Harvey L, Mendoza A, Simms D, Chouljenko VN, Wakamatsu N, et al. Impact and regulation of lambda interferon response in human metapneumovirus infection. Journal of virology. 2015;89(1):730-42. Epub 2014/10/31. doi: 10.1128/JVI.02897-14. PubMed PMID: 25355870; PubMed Central PMCID: PMCPMC4301146.

60. Mordstein M, Kochs G, Dumoutier L, Renauld JC, Paludan SR, Klucher K, et al. Interferon-lambda contributes to innate immunity of mice against influenza A virus but not against hepatotropic viruses. PLoS pathogens. 2008;4(9):e1000151. Epub 2008/09/13. doi: 10.1371/journal.ppat.1000151. PubMed PMID: 18787692; PubMed Central PMCID: PMC2522277.

61. Mordstein M, Neugebauer E, Ditt V, Jessen B, Rieger T, Falcone V, et al. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. Journal of virology. 2010;84(11):5670-7. Epub 2010/03/26. doi: 10.1128/JVI.00272-10. PubMed PMID: 20335250; PubMed Central PMCID: PMCPMC2876583.

62. Jewell NA, Cline T, Mertz SE, Smirnov SV, Flano E, Schindler C, et al. Lambda interferon is the predominant interferon induced by influenza A virus infection in vivo. Journal of virology. 2010;84(21):11515-22. Epub 2010/08/27. doi: 10.1128/JVI.01703-09. PubMed PMID: 20739515; PubMed Central PMCID: PMCPMC2953143.

63. Lukacikova L, Oveckova I, Betakova T, Laposova K, Polcicova K, Pastorekova S, et al. Antiviral Effect of Interferon Lambda Against Lymphocytic Choriomeningitis Virus. J Interferon Cytokine Res. 2015;35(7):540-53. Epub 2015/04/02. doi: 10.1089/jir.2014.0083. PubMed PMID: 25830339.

64. Ank N, West H, Bartholdy C, Eriksson K, Thomsen AR, Paludan SR. Lambda interferon (IFN-lambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo. Journal of virology. 2006;80(9):4501-9. doi: 10.1128/JVI.80.9.4501-4509.2006. PubMed PMID: 16611910; PubMed Central PMCID: PMC1472004.

65. Wen KW, Damania B. Kaposi sarcoma-associated herpesvirus (KSHV): molecular biology and oncogenesis. Cancer Lett. 2010;289(2):140-50. Epub 2009/08/05. doi: 10.1016/j.canlet.2009.07.004. PubMed PMID: 19651473; PubMed Central PMCID: PMCPMC4342847.

66. Djerbi M, Screpanti V, Catrina AI, Bogen B, Biberfeld P, Grandien A. The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors. The Journal of experimental medicine. 1999;190(7):1025-32. Epub 1999/10/06. PubMed PMID: 10510092; PubMed Central PMCID: PMCPMC2195646.

67. Duong FH, Trincucci G, Boldanova T, Calabrese D, Campana B, Krol I, et al. IFN-lambda receptor 1 expression is induced in chronic hepatitis C and correlates with the IFN-lambda3 genotype and with nonresponsiveness to IFN-alpha therapies. The Journal of experimental medicine. 2014. doi: 10.1084/jem.20131557. PubMed PMID: 24752298.

68. Honda M, Shirasaki T, Shimakami T, Sakai A, Horii R, Arai K, et al. Hepatic interferon-stimulated genes are differentially regulated in the liver of chronic hepatitis C patients with different interleukin-28B genotypes. Hepatology (Baltimore, Md. 2014;59(3):828-38. Epub 2013/12/07. doi: 10.1002/hep.26788. PubMed PMID: 24311440.

69. Fukuhara T, Taketomi A, Motomura T, Okano S, Ninomiya A, Abe T, et al. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. Gastroenterology. 2010;139(5):1577-85, 85 e1-3. Epub 2010/08/17. doi: 10.1053/j.gastro.2010.07.058. PubMed PMID: 20708617.

70. Karouni M, Kurban M, Abbas O. Plasmacytoid dendritic cells in skin lesions of classic Kaposi's sarcoma. Arch Dermatol Res. 2016;308(7):487-92. Epub 2016/07/04. doi: 10.1007/s00403-016-1671-6. PubMed PMID: 27372661.

71. Lasfar A, Lewis-Antes A, Smirnov SV, Anantha S, Abushahba W, Tian B, et al. Characterization of the mouse IFN-lambda ligand-receptor system: IFN-lambdas exhibit

antitumor activity against B16 melanoma. Cancer Res. 2006;66(8):4468-77. Epub 2006/04/19. doi: 10.1158/0008-5472.CAN-05-3653. PubMed PMID: 16618774.

72. Tezuka Y, Endo S, Matsui A, Sato A, Saito K, Semba K, et al. Potential anti-tumor effect of IFN-lambda2 (IL-28A) against human lung cancer cells. Lung cancer. 2012;78(3):185-92. Epub 2012/10/02. doi: 10.1016/j.lungcan.2012.09.005. PubMed PMID: 23021208.

73. Yan Y, Zhang J, Liu Y, Zhu T, Yuan L, Ge Y, et al. Inhibition of lung adenocarcinoma transfected with interleukin 28A recombinant adenovirus (Ad-mIFN-lambda2) in vivo. Cancer Biother Radiopharm. 2013;28(2):124-30. Epub 2012/11/09. doi: 10.1089/cbr.2012.1247. PubMed PMID: 23134221.

74. Zitzmann K, Brand S, Baehs S, Goke B, Meinecke J, Spottl G, et al. Novel interferon-lambdas induce antiproliferative effects in neuroendocrine tumor cells. Biochemical and biophysical research communications. 2006;344(4):1334-41. Epub 2006/05/03. doi: 10.1016/j.bbrc.2006.04.043. PubMed PMID: 16650825.

75. Hui X, Chen H, Zhang S, Ma X, Wang X, Huang B. Antitumor activities of recombinant human interferon (IFN)-lambda1 in vitro and in xenograft models in vivo for colon cancer. Cancer letters. 2011;311(2):141-51. Epub 2011/08/30. doi: 10.1016/j.canlet.2011.07.004. PubMed PMID: 21872388.

76. Li Q, Kawamura K, Ma G, Iwata F, Numasaki M, Suzuki N, et al. Interferon-lambda induces G1 phase arrest or apoptosis in oesophageal carcinoma cells and produces anti-tumour effects in combination with anti-cancer agents. Eur J Cancer. 2010;46(1):180-90. Epub 2009/11/03. doi: 10.1016/j.ejca.2009.10.002. PubMed PMID: 19879751.

77. Abushahba W, Balan M, Castaneda I, Yuan Y, Reuhl K, Raveche E, et al. Antitumor activity of type I and type III interferons in BNL hepatoma model. Cancer Immunol Immunother. 2010;59(7):1059-71. Epub 2010/03/11. doi: 10.1007/s00262-010-0831-3. PubMed PMID: 20217081; PubMed Central PMCID: PMCPMC4699672.

78. Sato A, Ohtsuki M, Hata M, Kobayashi E, Murakami T. Antitumor activity of IFN-lambda in murine tumor models. J Immunol. 2006;176(12):7686-94. Epub 2006/06/06. PubMed PMID: 16751416.

79. Numasaki M, Tagawa M, Iwata F, Suzuki T, Nakamura A, Okada M, et al. IL-28 elicits antitumor responses against murine fibrosarcoma. J Immunol. 2007;178(8):5086-98. Epub 2007/04/04. PubMed PMID: 17404291.

80. Cannella F, Scagnolari C, Selvaggi C, Stentella P, Recine N, Antonelli G, et al. Interferon lambda 1 expression in cervical cells differs between low-risk and high-risk human papillomavirus-positive women. Med Microbiol Immunol. 2014;203(3):177-84. Epub 2014/02/11. doi: 10.1007/s00430-014-0330-9. PubMed PMID: 24510368.

81. Regamey N, Cathomas G, Schwager M, Wernli M, Harr T, Erb P. High human herpesvirus 8 seroprevalence in the homosexual population in Switzerland. Journal of clinical

microbiology. 1998;36(6):1784-6. PubMed PMID: 9620422; PubMed Central PMCID: PMCPMC104922.

82. Liu Z, Fang Q, Zuo J, Chen Y, Minhas V, Wood C, et al. Global epidemiology of human herpesvirus 8 in men who have sex with men: A systematic review and meta-analysis. J Med Virol. 2018;90(3):582-91. Epub 2017/10/05. doi: 10.1002/jmv.24960. PubMed PMID: 28975631.

83. Gao SJ, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med. 1996;2(8):925-8. PubMed PMID: 8705864.

84. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med. 1998;338(14):948-54. doi: 10.1056/NEJM199804023381403. PubMed PMID: 9521982.

85. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet. 1996;348(9035):1133-8. Epub 1996/10/26. doi: 10.1016/S0140-6736(96)07560-5. PubMed PMID: 8888167.

Table 1. Independent risk factors associated with KS among MSM.

	Univariate		Multivariate	
Variable	**HR (95% CI)[1]**	**P**	**HR (95% CI)**	**P**
Age at estimated date of infection	1.01 (1.00-1.03)	0.07	1.05 (1.00-1.11)	0.07
$CD4^+$ nadir[2] (sqrt transformed,continuous)	0.99 (0.99-1.00)	**<0.001**	1.00 (0.99-1.00)	**<0.001**
$CD4^+$ slope[3] (continuous)	0.69 (0.58-081)	**<0.001**	0.84 (0.70-1.02)	0.07
Maximal HIV RNA load (continuous)	1.21 (1.01-1.44)	**0.04**	1.02 (0.84-1.24)	0.85
HAART (time-dependant covariate)	2.96 (0.74-11.93)	0.13	0.38 (0.26-0.55)	**<0.001**
HCV co-infection[4]	0.92 (0.55-1.53)	0.75		
Active HBV infection[5]	1.32 (0.78-2.24)	0.30		
SNPs				
IFNL3/4 rs12980275 (AA versus AG or GG)	1.36 (1.04-1.77)	**0.03**		
IFNL3/4 rs8099917 (TT versus TG or GG)	1.40 (1.07-1.82)	**0.01**		
Diplotypes				
No IFNL4	Reference		Reference	
IFNL4 P70	1.40 (1.05-1.87)	**0.02**	1.43 (1.06-1.93)	**0.02**
IFNL4 S70	1.09 (0.74-1.61)	0.67	1.06 (0.69-1.60)	0.80

HR stands for hazard ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus. Stepwise (i.e. backward) regression (P<0.2) was used to determine which variables were independently associated with the endpoint.

[1] The proportional hazard assumption was verified for all variables with the exception of $CD4^+$ slope. However, the association between IFNL4P70 and KS was similar when $CD4^+$ slope was removed from the multivariate model (HR 1.33, 95% CI 1.07–1.65, P=0.01)

[2] The $CD4^+$ nadir square root was used to obtain a normally distributed variable

[3] Rate of $CD4^+$ depletion in the absence of HAART

[4] Reflected by HCV serology

[5] Defined by the presence of HBsAg in the blood

Figure legend

Figure 1. Cumulative incidence of Kaposi's sarcoma according to IFNL4 *rs12980275* (A), IFNL3/4 *rs8099917* (B), IFNL4P70 (C) in MSM participants of the SHCS. The estimated date of HIV infection was used as a starting point with censoring at death or lost follow-up. (n) indicates the number of patients with KS in each group of patients. P values were calculated by log-rank test, dominant mode.